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10/594200

SMALL MOLECULE ANTAGONISTS OF XIAP FAMILY PROTEINS

*This Appl. is a 371 of 02/7/05/07/317 FILED 3/22/05 which claims
Field Of The Invention benefit of 01/5/05/263 FILED 3/22/04.*

[0001] The present invention relates to naturally occurring and chemically synthesized small molecule antagonists of XIAP family proteins. In particular, the present invention provides embelin and other XIAP inhibitors and methods of using these compounds as antagonists of the anti-apoptotic effects of XIAP family member proteins. The present invention also provides methods for treating diseases and pathologies (e.g., neoplastic diseases).

Background Of The Invention

[0002] Multicellular organisms use a process called apoptosis to instruct damaged or unnecessary cells to destroy themselves for the good of the organism. Control of the apoptotic process is very important for the normal development of the organism. For example, fetal development of fingers and toes requires the controlled removal, by apoptosis, of excess interconnecting tissues, as does proper formation of neural synapses within the brain. Careful control of apoptosis is also important to adult organisms, for instance, controlled apoptosis is responsible for the sloughing of the inner lining of the uterus (the endometrium) at the start of menstruation.

[0003] Apoptosis not only plays an important role in tissue sculpting during fetal development and normal cellular maintenance, it is also the primary defense against rogue cells that threaten the well being of the entire organism. For instance, in the cell-mediated immune response, effector cells (e.g., cytotoxic T lymphocytes "CTLs") destroy virus-infected host cells by inducing the infected host cells to undergo apoptosis. The organism subsequently relies in turn upon the apoptotic process to destroy the effector cells when they are no longer needed. Autoimmunity is prevented by the CTLs inducing apoptosis in each other and even in themselves. Defects in this process are associated with a variety of autoimmune diseases such as lupus erythematosus and rheumatoid arthritis.

[0004] Multicellular organisms use the apoptotic process to instruct cells with damaged nucleic acids (e.g., DNA) to destroy themselves prior to becoming cancerous. However, some cancer-causing viruses prevent apoptosis in transformed cells. For example, several human papilloma